III. PHARMACOLOGY OF NICOTINE

There is a vast literature on this subject, which dates back into the early nineteenth century. Nicotine has a multiplicity of actions, which are highly dose-dependent. Overall responses may therefore appear paradoxical. The complexity of the responses and their dose dependency probably conduce to the expression of individual differences among human subjects, dependent on the relative reactivities of their various systems as determined by genetic factors as modified by life experience.

In low concentrations, nicotine has a stimulating action on certain chemoreceptors which initiate reflexes affecting many parts of the body. The most important of these are the receptors of the carotid and aortic bodies. Somewhat higher concentrations can stimulate both the sympathetic ganglia and the parasympathetic ganglia while still higher concentrations block or paralyze ganglionic transmission. Since sympathetic and parasympathetic nerves in general mediate opposite effects, these dual effects of nicotine can contribute to the appearance of paradoxical responses. The interpretation of the effects of nicotine is further complicated by the fact that it stimulates the release of epinephrine from the adrenal medulla and from other depots. The effects of this hormone on the circulation resemble in many respects those of nicotine itself.

A persistent and very practical problem is to appraise the significance of responses that human subjects may show from such nicotine absorption as occurs within the range of that normally received from ordinary tobacco use. Failure to so appraise the results of animal experiments conducted with higher dose ranges has led to many questionable extrapolations in the past.

Comroe has suggested the possibility that all the actions of nicotine inspired in tobacco smoke on the circulation and respiration may be brought about by the stimulating effect of nicotine on certain chemoreceptors, below the amounts having ganglionic action.

It must be noted also that all pharmacological effects of nicotine are very transient, because of the rapid metabolism and excretion of this alkaloid, and that no chronic or cumulative effects have been reported. On the other hand, some recent epidemiological studies have reported a higher death rate from several cardiovascular diseases among smokers, particularly cigarette smokers, as compared to non-smokers.

One problem is to attempt to determine which, if any, responses to smoking, harmless to normal individuals, might present a hazard to individuals with an already severely damaged cardiovascular system.

Kalow has described the net circulatory effects of nicotine on heart rate and blood pressure, despite the multiplicity of actions, as comparable to those of exercise: "The stimulation produced by smoking one cigarette is not more than that caused by a modest effort." One approach to the problem of patient management may therefore be consideration of his tolerance of "modest physical effort" while the search for any more relevant effect specific to nicotine is continued.

Agress, employing a newer "vibrocardiographic" method of analyzing heart action, has compared responses to cigarette smoking with those following standardized exercise. He reports that the effects of smoking are equivalent to those from light exercise.

Within the context of the remarks above, abstracts of several cogent papers on "general pharmacology of nicotine" are appended.

Effects of Nicotine on
Coronary Artery Flow

Several studies on this subject have been sponsored by the Tobacco Industry Research Committee. These were made possible by the development of new techniques, first those employing catheterization of the coronary sinus and later those employing closed-chest methods. Similar studies have been made by investigators under other sponsorship.

Bargeron and collaborators showed by catheterization techniques that cigarette smoking in subjects without heart disease results in a significant increase in coronary blood flow and heart rate, and a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose.

Forte and collaborators made similar observations on anaesthetized dogs into which nicotine was infused.

Kien and collaborators confirmed these coronary flow observations on dogs but reported also a "brief but marked" increase in the oxygen saturation of venous blood following nicotine, which they regarded as reflecting a transient decline in cardiac oxygen utilization which was manifested also in the electrocardiogram.

Bellet and collaborators confirmed the lack of coronary vaso-constriction in dogs, following systemic nicotine administration, and proceeded to coronary artery injections of nicotine to elucidate direct cardiac effects independent of systemic changes. Parasympathomimetic, sympathomimetic and Bezold-Jarisch responses were observed.

An approach to the study of nicotine effects in coronary insufficiency has been made by Bellet and collaborators using dogs with coronary arterial ligation. Nicotine increased cardiac work markedly in both normal and ligated dogs. Coronary flow was increased by nicotine but the degree of increase was inversely related to the degree of coronary narrowing to the point of disappearance. Coronary vascular resistance and myocardial oxygen utilization declined during nicotine administration.

Bing and his collaborators have reported a series of studies contrasting the responses to nicotine by normal subjects and by patients with coronary disease. During cigarette smoking, both groups had significant acceleration of heart rate, a rise in arterial pressure (except in one coronary patient) and in left ventricular work but no significant change in coronary blood flow. Oxygen usage by the heart remained virtually unchanged. There was no evidence of ischemia in the coronary patients. The increased coronary flow, observed previously in normals after smoking, and the lack of such response in coronary artery disease patients, suggest that the latter may be limited in their capacities to expand coronary flow.

Nicotine and the Peripheral Circulation

While this subject has been studied extensively in the past, considerable new knowledge has been obtained recently by more refined studies. Oppenheimer demonstrated long ago that a distinction must be drawn between influences that modify blood flow in the skin and those which affect the deeper circulation. Effects are often opposite on these two vascular beds.

Most recent investigations indicate that the inhalation of tobacco smoke reduces blood flow in the skin, especially of the toes. Wood has confirmed this response but has shown that in comparison, cooling the environment has a much more marked effect.

Conversely, smoking caused a moderate vasodilation in skeletal muscle (Reuf, Rottenstein et al.).

Eckstein, Coffman and their collaborators have measured the reactive hyperemia of the foot following venous occlusion. Smoking two cigarettes decreased this reactive hyperemia; on the other hand, cooling the environment produced a more consistent decrease.

Venous pressure-volume curves have been measured plethysmographically in the forearm of healthy men by Eckstein and collaborators. Intravenous nicotine administration produced venous constriction in nearly all, while venous pressure changes were not consistent.

Freund has reported a series of studies on the effects of sham and actual smoking on the peripheral circulation of normal subjects and of patients. Pulse rates increased after smoking but did not correlate with plethysmographic changes. Smoking generally produced significant fall in skin temperature, in radiosodium clearance and in venous oxygen saturation in normals, but such changes did not occur in patients with peripheral vascular disease. There were also marked individual variations in plethysmographic changes in both groups.

Because changes in the skin flow in the extremities may mask changes in skeletal muscle flow, Coffman and collaborators clinically studied the latter, as affected by smoking, by using the disappearance rate of a radioactive isotope from skeletal muscle of the calf. Fourteen of seventeen normal subjects showed an increase in skeletal nutritive blood flow during smoking, despite the usual decreases in skin temperature. An intact nervous supply to the limb is not necessary to the response since three of four sympathectomized limbs showed the same increased flow.

A review on the Effect of Nicotine and Tobacco on Muscle Function by Fischer, Silvette, Larson and Haag considers reported effects of nicotine in wide variety but concludes that human muscular efficiency is very much more influenced by psychological than by physiological factors and that so far as the ordinary smoker is concerned, there is little or no untoward effect of the practice on skeletal muscle function.

Nicotine and the Central Nervous System

Schmitterlöw and Hansson have shown that when C^{14} tagged nicotine is injected intramuscularly into mice it is rapidly concentrated in the brain and spinal cord.

Domino has reported an action by nicotine on the ascending reticular activating system of the brain in dogs, which he believes is direct rather than mediated through epinephrine, nor-epinephrine, 5-hydroxytryptamine or vasopressin, though not all possibilities for mediation have been ruled out. This effect occurs with blood levels of nicotine such as are commonly achieved in tobacco use by man. At present rat studies are underway to explore the behavioral consequences of the effect. Very small subcutaneous doses of nicotine appear in preliminary studies, to increase slightly the learning rate for rats in a conditioned avoidance situation.

Nicotine and Serum Free Fatty Acids

Bellet and collaborators have reported that the smoking of two cigarettes by human subjects, including normals, heart cases and patients with other diagnoses, was followed by a brief elevation in serum free fatty acids. Since this is a well-known effect of epinephrine, it seems most likely that this response to smoking is mediated through epinephrine release by nicotine. Total serum cholesterol or triglycerides were not affected.

The response was not related to age, sex, previous smoking habits, type of cigarette or pre-smoking levels of free fatty acids. It was more marked in subjects with healed myocardial infarctions. Non-smoking controls subjected to idential venipuncture and other procedures also experienced a moderate but smaller increase in free fatty acids.

It has not been determined whether the exaggerated response of coronary patients is a result of their disease or reflects a pre-existing hyper-reactivity to stress.

Whether such transient free fatty acid elevations, occurring frequently, could influence the atherosclerotic process is a matter of speculation; the animal experiments superimposing long-term nicotine administration upon atherogenic diets do not lend much support to such a conjecture. (See Topic IV.)

Immunological Aspects of Tobacco Use

The question was raised long ago whether the "purely pharmacological" effects of nicotine or smoking might be complicated by superimposed responses due to allergic hypersensitivities in some individuals.

A general critical review of the subject has been published by Silvette, Larson and Haag, which concludes that experimental work on immunology to tobacco has been fragmentary and that a complete classic immunological study of tobacco is urgently required, not only for its own sake but as a basis for evaluating concepts of tobacco's possible role as an etiological agent in disease.

Such investigations have been undertaken by Sulzberger, Redisch, Fontana, and their collaborators. In a series of papers they report that patients who have symptoms which might be attributed to smoking, such as cough or disturbance of the peripheral circulation, show a higher incidence of skin sensitivity to tobacco extracts than do others. These studies continue.

Circulatory Effects of Pipe and Cigar Smoking and of Tobacco Chewing

Limited studies by Simon and collaborators have shown that the circulatory effects of pipe and cigar smoking and of tobacco chewing are similar in nature to those produced by cigarette smoking and hence are probably attributable to nicotine absorption. Transient increases in pulse rates and in systolic and diastolic blood pressures generally occurred, while a drop in skin temperatures of fingers and toes was general. Ballistocardiograms were altered in many of the older subjects but usually not in the younger ones.

According to Simon, the effects of cigar and pipe smoking were generally less marked than those of cigarette smoking or tobacco chewing.

Larson, however, has summarized the observations of several investigators on nicotine absorption from various forms of tobacco use. Some have concluded that more nicotine is absorbed from cigar smoke, even without inhaling, than from cigarette smoke. Absorption is related to moisture content of the cigar and alkalinity of the smoke.

These observations seem especially important for consideration in relation to the marked differences found in epidemiologic studies with respect to the reported low cardiovascular death rates among pipe and cigar smokers as compared to those among cigarette smokers. It appears doubtful whether differences in measurable cardiovascular responses to these various forms of tobacco use are adequate to explain such marked epidemiological differences.

Studies currently underway are attempting to refine the measurement of the relative nicotine absorption from actual cigarette, cigar and pipe smoking.

Experiments on the effects of nicotine administration to animals on atherogenic diets are discussed under Topic IV.

IV. INITIATING VERSUS DEVELOPMENTAL INFLUENCES

General Comments

It is obviously difficult to separate influences on the initiation of cardiovascular diseases and those which affect the development of such diseases once they are established.

This is especially true where recognition and classification of the disease occur only after other symptoms exist, as is usually the case.

As might be expected, there is no hard and fast rule or universally consistent clinical opinion on this matter. It is clear that individuals differ in response to smoking and to their deprivation from the habit.

Further research may conceivably indicate that a sufficiently high percentage of those with established degrees of cardiovascular disorders will react so unfavorably to smoking as to justify medical advice on certain courses of restrictive action. This, however, is properly a matter of relationship between the individual doctor and his patient. The desired situation is one which will involve as broad and comprehensive knowledge as can possibly be acquired to guide the profession in the light of its clinical experience.

The references appended will present opinions which are based on such experience. They should be considered as being contributory rather than conclusive and as being selected for purposes of comparison.

The important point is that more refined and sophisticated longitudinal studies of controlled populations of apparently normal individuals are sorely needed. These should aid in refining our recognition of departures from normalcy which represent the earliest evidence of the diseases under study and which, therefore, may be closely connected with their origin.

Similarly, manipulable populations of patients with established early cardiovascular diseases should provide material for more sophisticated clinical studies of factors which may influence the progress and course of these diseases.

Until such studies are organized and bear fruit we shall have to be content with a type of evidence which leaves doubt as to whether we are dealing with factors which influence origin alone, progressive development alone, or both.

Ocular, Cerebral and Other Peripheral Circulation

According to Bettman, Fellows, et al., the effect of cigarette smoking on intraocular blood volume in man is not known. They have, therefore, used animals for experimentation.

If the cigarette was smoked at the normal rate there was no effect. If it was smoked rapidly there was a significant rise in intraocular volume. Denicotinized cigarettes gave generally similar results.

In one rare arterial disease (thromboangiitis obliterans-arteriosclerosis obliterans) prognosis is improved (Boake and Barnet) by abstinence from tobacco. In atherosclerotic patients with intermittent claudication, there was no effect of smoking on the blood flow of the calf or foot. Abramson found no evidence that smoking affected progression of this disease. Selvaag et al. report similar results in Norway.

Hypertension

There is little evidence that smoking causes hypertension.

Actually D'Alonzo found that in employees of the E. I. DuPont de Nemours and Co. there was a higher prevalence of hypertension in non-smokers than in smokers. Hines finds no effect of smoking on the resting blood pressure. Similar results are reported by Hitchens.

Lower prevailing levels of blood pressures in smokers as compared with non-smokers have been reported by a number of investigators. Among these may be mentioned two papers by Brown et al. in England; a paper by Orma et al. and one by Karvonen, Orma et al. in Finland; and two by Blackburn et al. in the United States.

Cholesterol Levels

This is of course a subject on which there is a voluminous literature. According to various authors cholesterol levels appear to be affected by a number of factors such as diet, heredity, age, sex, stress and smoking.

Sufficiently well-planned and sophisticated clinical studies to analyze these variables or even to establish an adequate baseline of "normalcy" for range of cholesterol levels by age and sex are conspicuous by their absence.

Since there is no apparent consistent relationship between amount of smoking (Konttinen et al., Orma et al., Page et al.) and changes in cholesterol level, it would seem that no final conclusions are wise at this time.

On the other hand, there is sufficient evidence of a relationship between smoking and cholesterol level in certain individuals and in certain groups to offer a most intriguing field for further studies. For example, could the type and/or the degree of change in cholesterol levels be better analyzed by the use of smoking vs. non-smoking as a possible differential factor during the lifetime of various individuals observed under established and controlled conditions? Might not such observations help to analyze some of the individual host responses to the different factors which influence cardiovascular diseases?

Rather than over-organize the reports of research in the field of cholesterol levels, there are included references to and excerpts from a number of papers not specifically mentioned in this brief discussion, and yet of possible interest in connection with it.

Atherosclerosis

Studies on the possible relation between smoking and atherosclerosis have been included in several of the groups of excerpts which are being forwarded.

It will be well to repeat the recommendation that evidence for or against etiological effects should be carefully distinguished from that bearing on progress of the already established diseases. Both aspects are important but their implications may be quite distinct and different in evaluating the potentialities and form of action of any suspected agent of habit such as smoking.

In this connection, Baltin comments on aggravation of coronary disease and Calataynd et al. on factors in its origin, in a population of Trappist monks.

As a matter of possible interest, a suggestion that density of population among the birds and mammals in the Philadelphia Zoological Gardens has been the main factor in a marked increase in coronary disease recorded at autopsy has been made by Ratcliffe. Although obviously smoking habits can be ignored, the possible bearing of this theory on human urbanization or overcrowding is worth mention in passing.

Animal Experiments Involving Nicotine Administration

The question whether repetitive small absorptions of nicotine, in view of its rapid elimination and metabolism, can produce any persisting effects, has been mentioned elsewhere. Several animal investigations have been conducted with a view to determining whether superposition of nicotine administration upon an atherogenic diet would modify or accelerate the development of arterial disease.

Wenzel has reported such studies on rabbits and hens, with use of high cholesterol diets to which graded doses of nicotine were added up to the "equivalent of two packs of cigarettes daily." The nicotine addition did not affect body weight, serum cholesterol levels, lipid phosphorus or gross aortic atherosclerosis. Electrocardiographic changes under ergonovine stress, were at first regarded as indicating more extensive pathologic changes. However, omission of ergonovine use in stress-testing the animals in vivo, virtually eliminated any anatomic difference between nicotine-treated and untreated animals, observable on autopsy. Hence the results appear to be equivocal.

Later experiments by Wenzel are reported as showing no effect of nicotine administration upon plasma cholesterol, lipid phosphorus or c/p ratios at higher cholesterol administration levels, but a significant increase by nicotine of these plasma components when dietary cholesterol was relatively low.

Because of the artificial nature of these rabbit experiments, and the doubtful analogy between atherosclerosis in man and such induced atherosclerosis in rodents, the interpretation of these results in terms of human experience is difficult.

Travell and collaborators have shown that the normal enhancement by nicotine, of coronary artery blood flow in the isolated rabbit heart is not found in atherosclerotic rabbit hearts. A similar difference in the effects of norepinephrine was also observed.

Bellet and collaborators have reported that daily intramuscular injections of nicotine bitartrate, in a delayed absorption medium, into mongrel dogs was followed by a gradual increase in mean serum cholesterol levels, which attained a peak at the end of four weeks and was maintained for two more. There was no change in mean serum triglycerides.

Haag and collaborators have subjected weanling rats to cigarette smoke inhalation at half hour intervals, fourteen times a day for practically their entire life span, with two groups of controls. The smoked animals had the same average life span as controls, slightly lesser weight and the same prevailing blood pressures during non-exposure periods despite brief elevations in blood pressure immediately after smoking. The authors point out "the need for writers in this field to describe in sufficient detail the materials and techniques employed in their work to allow reasonable comparisons with other animal studies of similar nature, and with the conditions existing in human smoking."

Angina

Most authors agree that smoking is rarely, if ever, a precipitating factor in angina pectoris.

Conn and Kissane (1958) and Green and Borousch (1960) as well as Master (1956) all recommend a discriminatory point of view based upon study of the individual angina patient as the proper determiner of the nature of advice to be given him.

Buerger's Disease - Raynaud's Disease

In Raynaud's disease, restriction of tobacco does not appear to influence morbidity according to Gifford (1958). There is some evidence according to Peacock (1958) that mental stress -- at times associated with menopause or childbirth -- is an etiological factor in 50% of 42 cases. In the other 21 cases "no such etiological factors could be detected." Smoking is not mentioned.

It may also be noted that Barnett and Boake (1960) observed no consistent change in blood flow of the calf in legs of six adult males affected by atherosclerosis.

An abstract by Abramson (1963) of a recent book on Buerger's Disease by DeBakey and Cohen reviewing World War II cases, states that "the relationship between smoking and the etiology of the disease was not sufficiently clearcut to be conclusive." It further mentions that "the study did not support the impression that abstinence from smoking caused amelioration of symptoms or a decrease in the necessity for amputation."

In recent years there has been some debate as to whether Buerger's Disease is really a clinical entity distinct from peripheral vascular atherosclerosis. McKusick, with the aid of a Tobacco Industry Research Committee grant, has made a new study of this disease among young men in an Oriental country, where it is relatively more prevalent than in the United States, and has concluded that the syndrome as encountered there is distinct from generalized atherosclerosis or embolism of the peripheral vasculature. While all the sixty-two patients he observed were smokers, the study suggested strongly that the etiology and pathogenesis of the disease are probably complex and indicated that it still remains to be proved whether the essential lesion is truly an angiitis.

Miscellaneous Specific Relationships

Bing and his associates have, as previously mentioned, studied smoking and coronary blood flow, myocardial oxygen consumption, cardiac output and ischemia in normal patients and in those with coronary disease. Their results indicate no seriously deleterious effects but should be evaluated by firsthand study of the papers.

Freund (1957) shows no change in arterial or venous lactic acid, and Rehder and Roth (1959) no rise in the level of fasting blood sugar or in epinephrine-like substances of venous blood following smoking.

Bellet and collaborators have reported that nicotine infusion into dogs produces an increase in the fibrinolytic activity of their blood plasma. Human subjects are now being studied similarly.

No deleterious effect on ascorbic acid metabolism following smoking could be found by Taber and Larson (1962) in contrast to reports by McCormick.

Coagulability of blood was not affected by smoking according to Blackburn et al. (1959).

Davidge (1955), having studied 92 consecutive cases of myocardial infarction, stated, "there appears to be no relationship between the use of cigarettes and the occurrence of mortality" from that disease.

A conservative evaluation of smoking was made by Hunt (1956) who said, "it is hard to believe that smoking in moderation always makes coronary disease worse." Ellis and Hancock (1957) believe that "a physician should evaluate very carefully how important it is to restrict (by forbidding smoking) the happiness of a patient (coronary artery disease) who is already limited in so many ways."

Keys (1955) is much more assertive. He states, "I believe there is already evidence at hand to disprove the hypothesis that smoking has an important primary effect in the development of coronary heart disease;" and Hellerstein and Ford (1957), in a paper on rehabilitation of the cardiac patient, say that "the categorical denial of tobacco to all patients must be condemned vigorously... Most patients with heart disease can smoke safely without apparent harm."